Pap Smear Update and Review

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Objectives

- Comprehensive Overview of Pap Smears
- Understand the normal and abnormal cervix in regards to the anatomy, cytology, and histology
- Review the Bethesda Pathology System
- Recognize the role of human papilloma virus in cervical carcinogenesis
- Triage of abnormal pap smears to colposcopy and follow-up

Pap Smears

- Carcinoma
- Precursors to Carcinoma
- HPV Infections

Pap Test Characteristics

- Simple
- Fast
- Painless
- Inexpensive
- Without Complications
- High Degree of Detection Rate

Pap False Negatives

- 5-50%
- 80% are True False Negatives
- 20% are Lab Errors

Pap Test False Positives

- 3-15%
- Overreading or mistaking benign cells for precancerous cells

Screening Characteristics

Relationship between Test Results and Disease

	Disease	No Disease
Test Positive	A	B
Test Negative	C	D

Sensitivity = A/(A+C) Testing positive/disease present

Specificity = D/(B +D) Testing negative/disease absent

False Positive % = B/(A+B) Testing positive/disease absent

False Negative % = C/(C+D) Testing negative/disease present

Pap Test as a Screening Tool

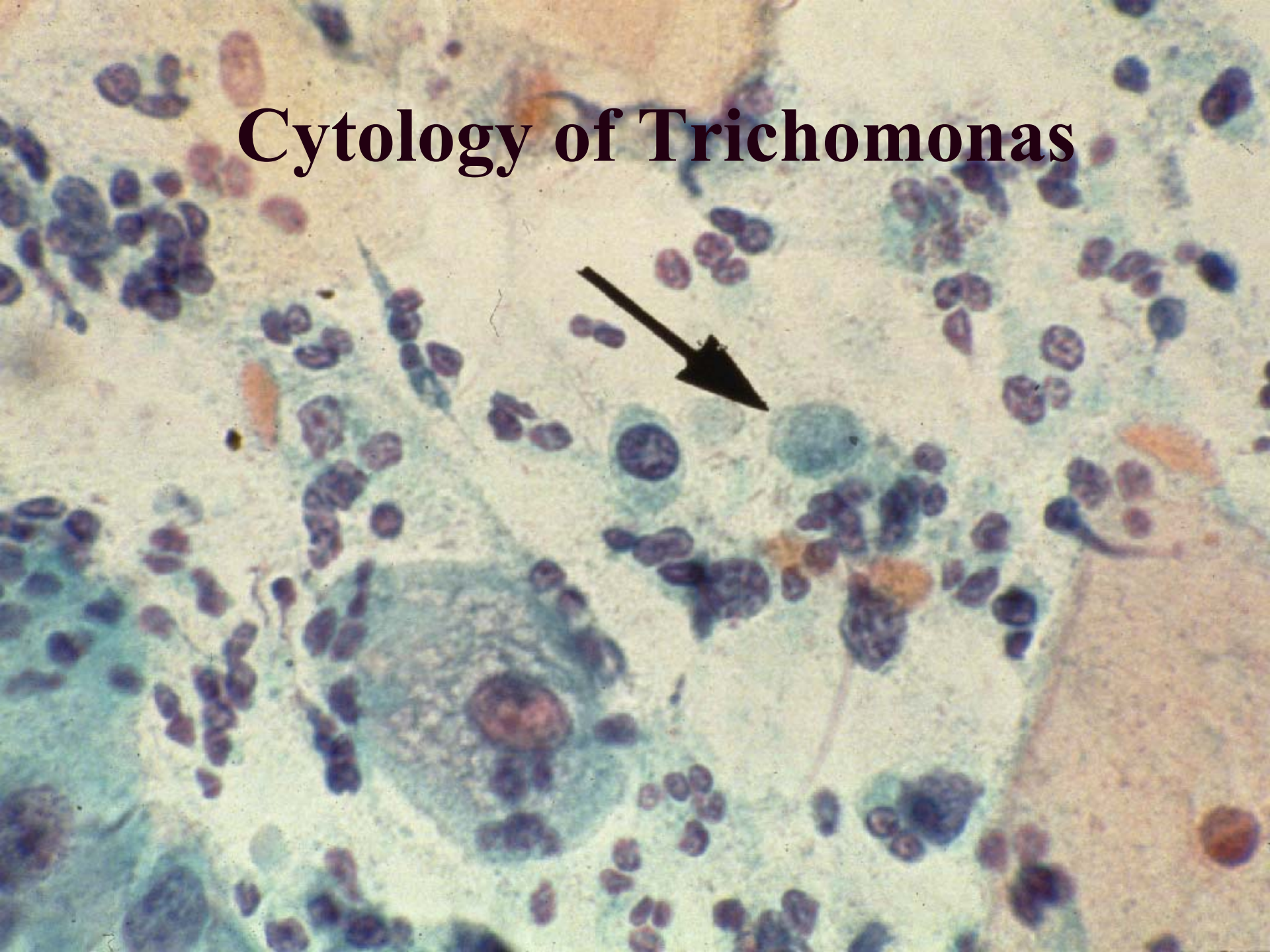
- Sensitivity
  - Moderate: 51–88%
- Specificity
  - High: 95–98%

Source: Meyers et al., 2000

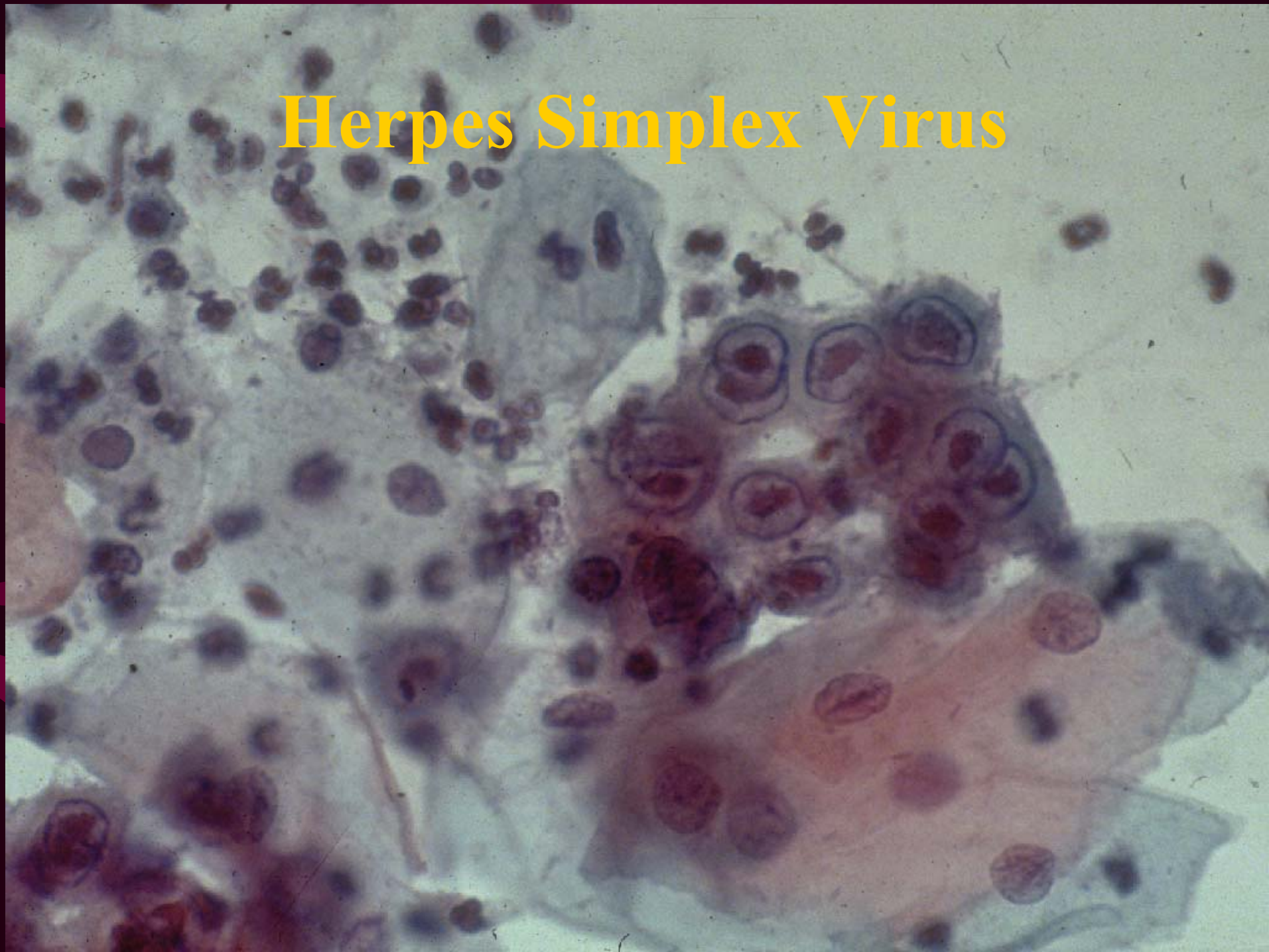
Reliability of Specific Diagnosis on Paps

- Herpes: Very Specific
- Yeast: Very Specific
  - Only Treat if Symptomatic
- Bacterial Vaginosis: Mostly Specific
  - Treat only if Symptomatic
  - Treat in Pregnancy
- Chlamydia: Very Non-specific
  - Never treat Chlamydia by Pap
  - Not a reliable pathologic diagnosis
- Trichomonas: Reliable about 85% of the time

Cytology of Trichomonas



Herpes Simplex Virus

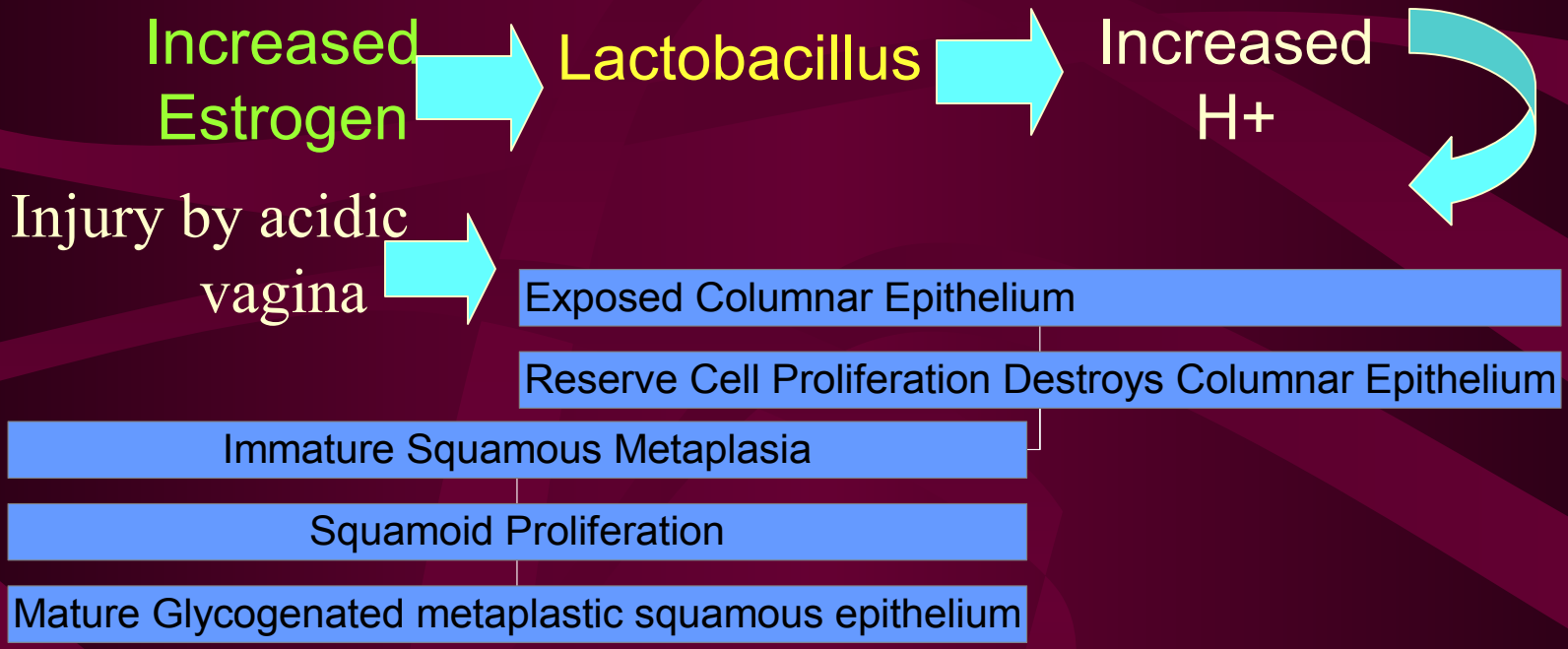


Normal Cervix

- Anatomy
- Original Squamous Epithelium
- Columnar Epithelium
- Immature Squamous Metaplasia
- Mature Squamous Metaplasia
- Transitional Zone

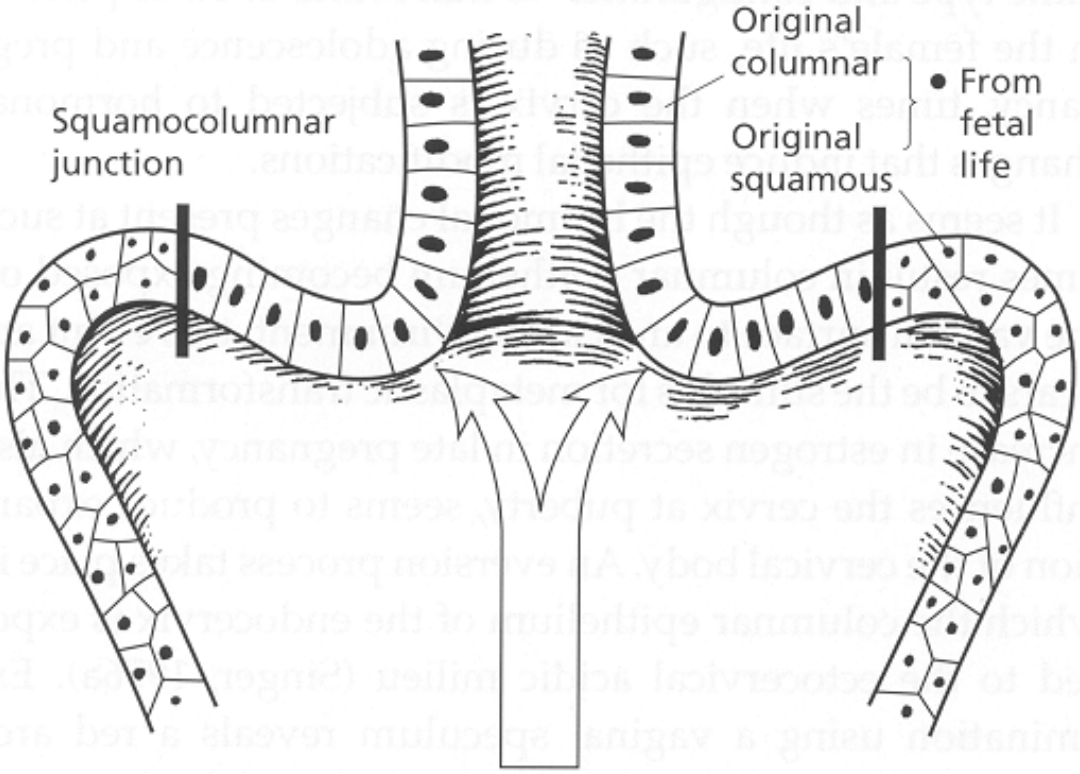
Normal Cervix

Physiologic process of Squamous Metaplasia



Normal Cervix

1 **Original epithelia**



2 **Metaplastic squamous epithelium**
Typical transformation zone
- Late fetal life
- Adolescence
- Pregnancy

3 **Abnormal (atypical) epithelium**
Atypical transformation zone
- Adolescence
- Pregnancy
- ? Other times

Includes (immature metaplastic squamous epithelium)
Cervical intraepithelial neoplasia 1–3, early invasion

Squamocolumnar Junction

- Original and “New”
- Transitional zone is area between
  - Greatest potential for neoplasia
- Adequate Colposcopy

Various Instruments

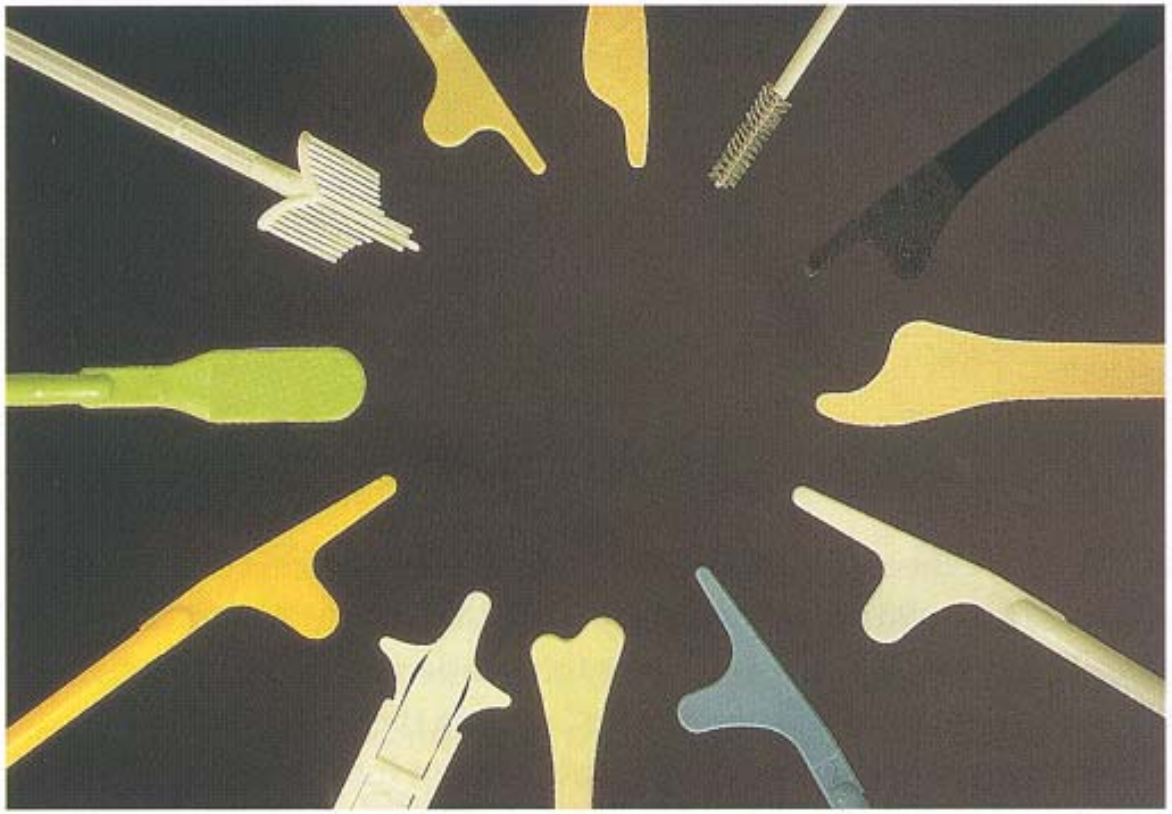
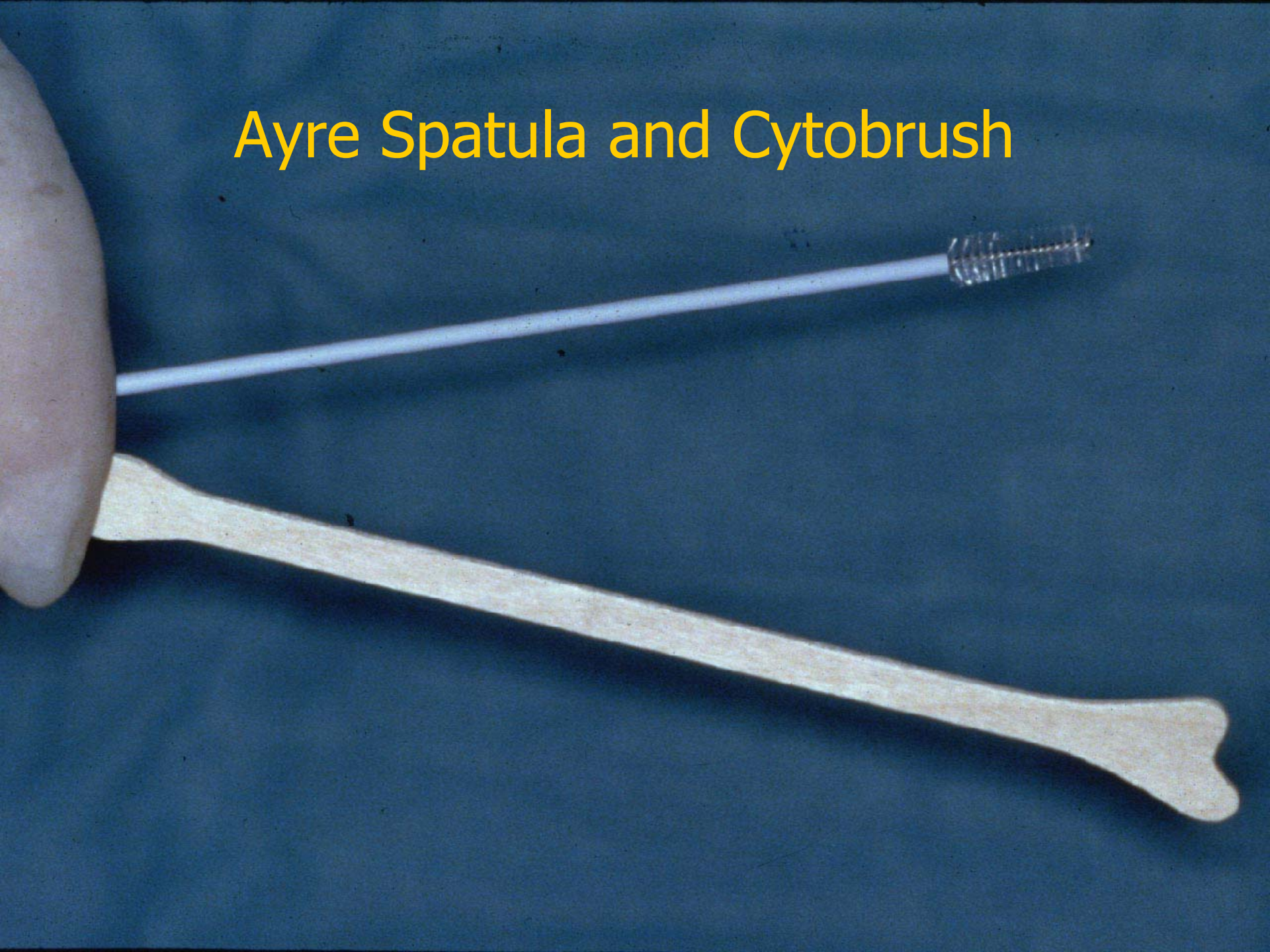
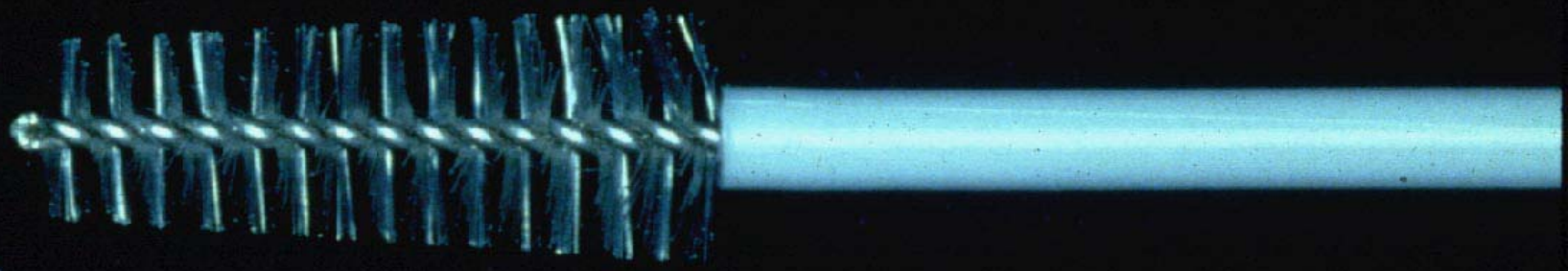


Fig. 5.5 A variety of wooden and plastic spatulas. All of these devices may be used to take smear samples. A critical component is the sampling technique used which requires correctly passing a speculum and visualizing the cervix.

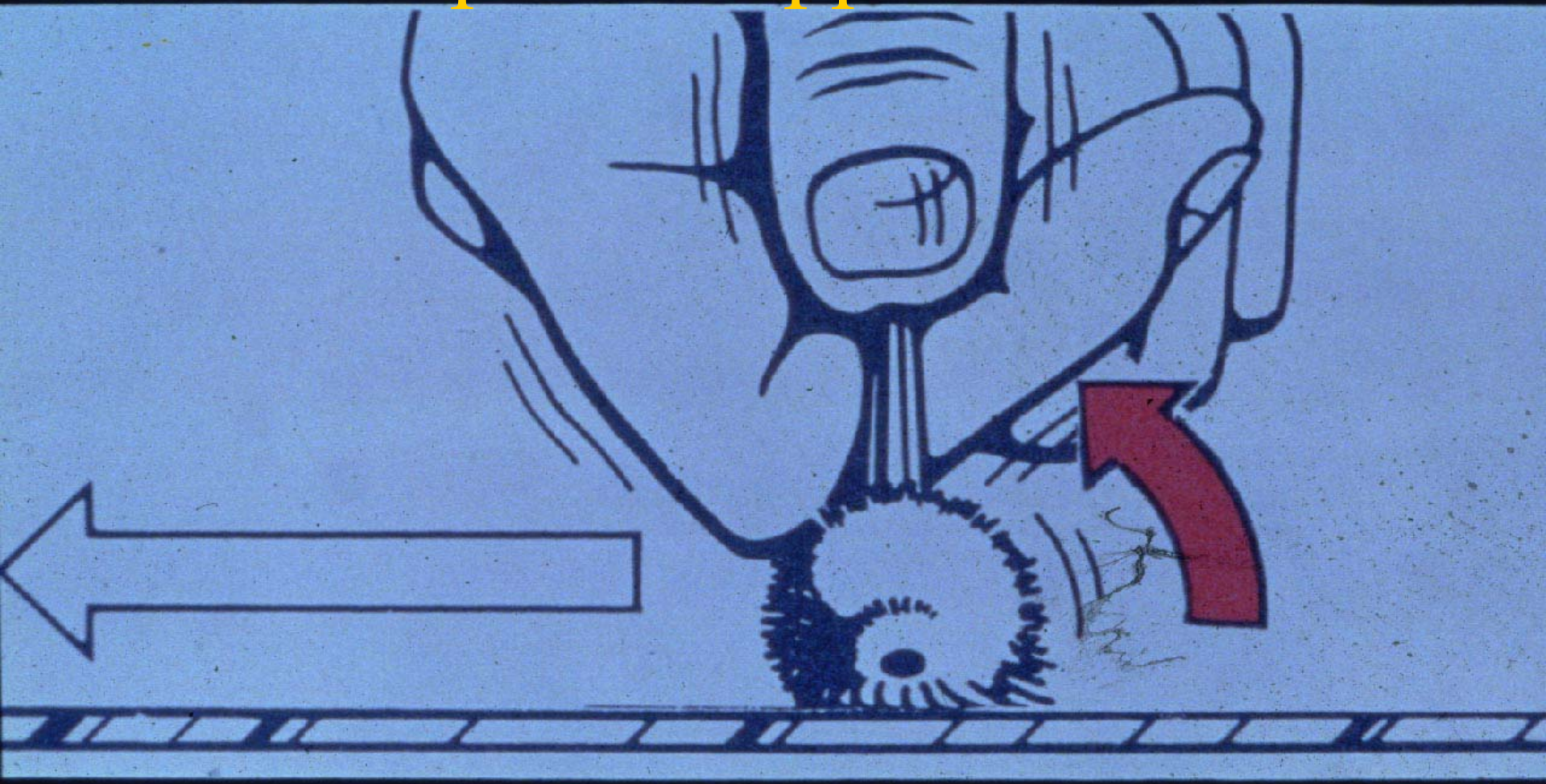
Ayre Spatula and Cytobrush

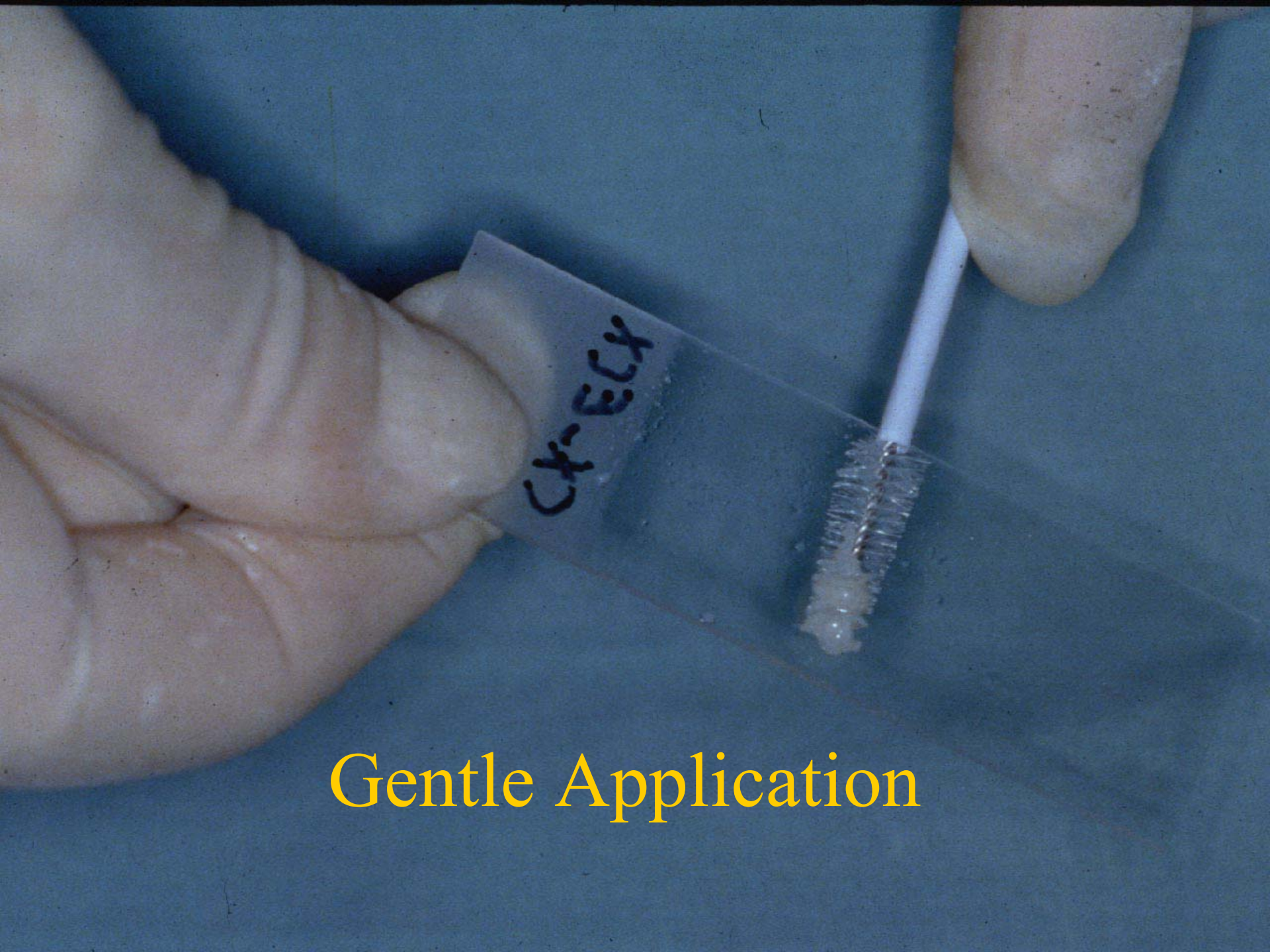


Endocervical Cytobrush



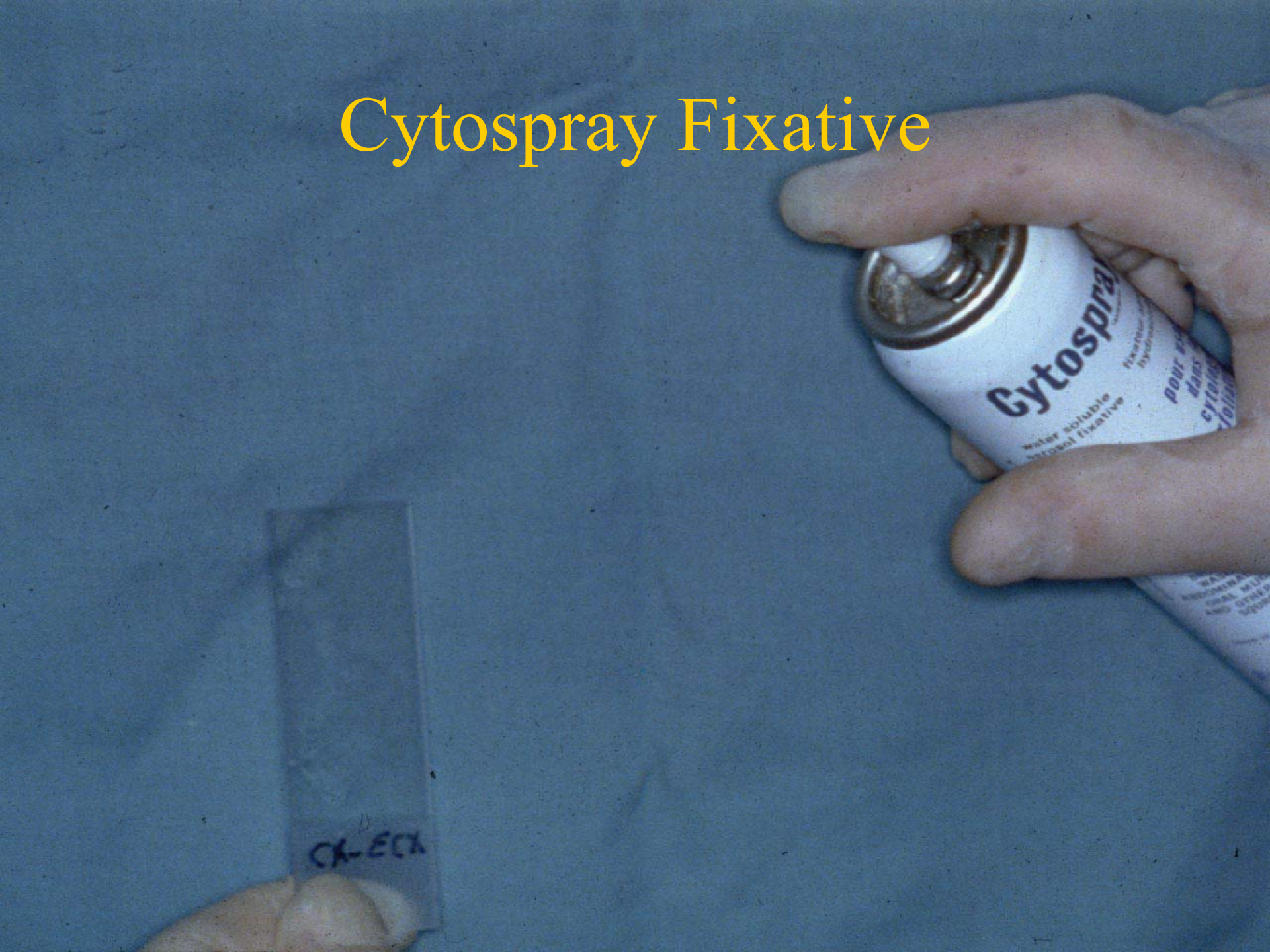
Optimal Application

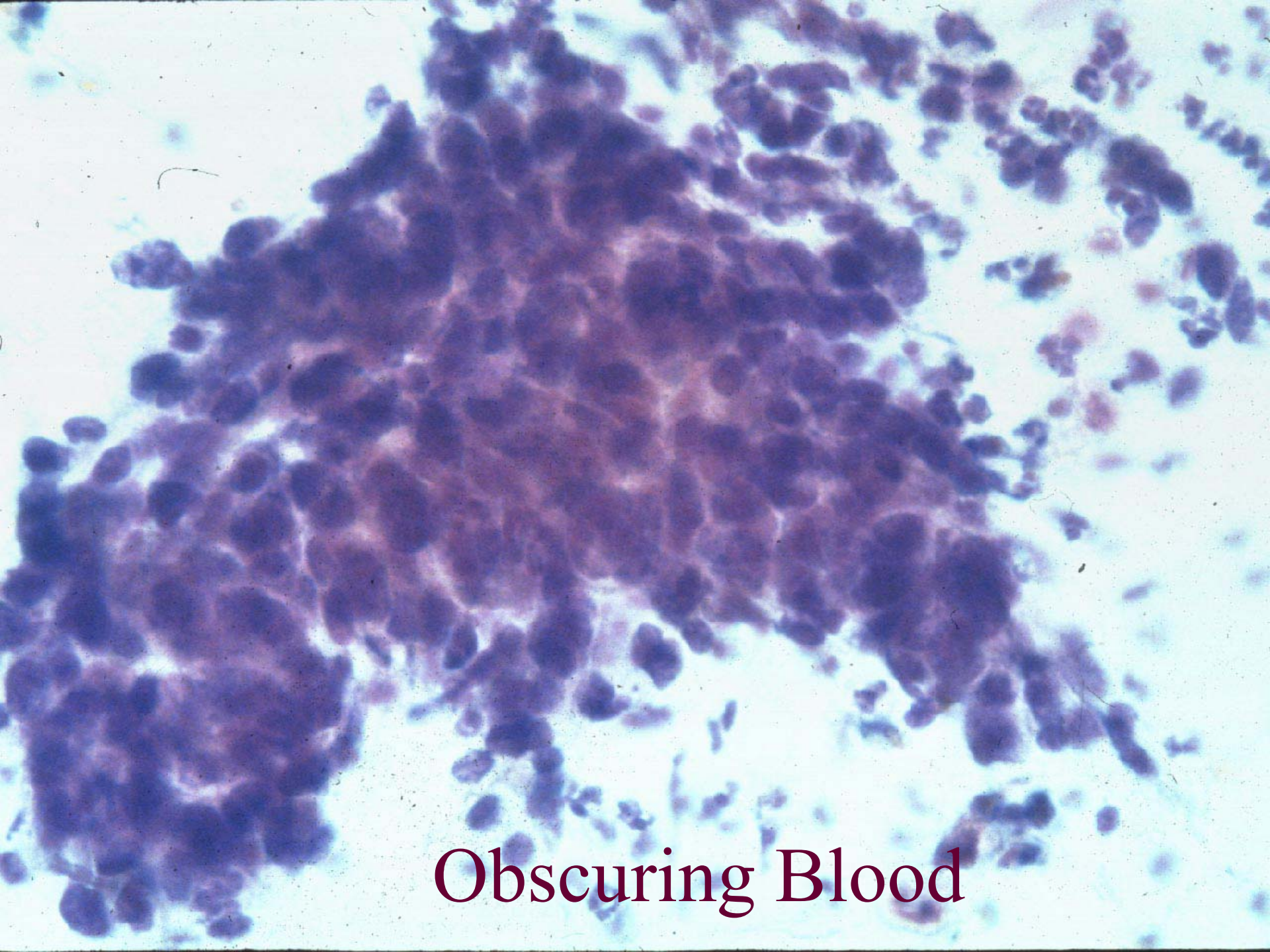




Gentle Application

Cytospray Fixative

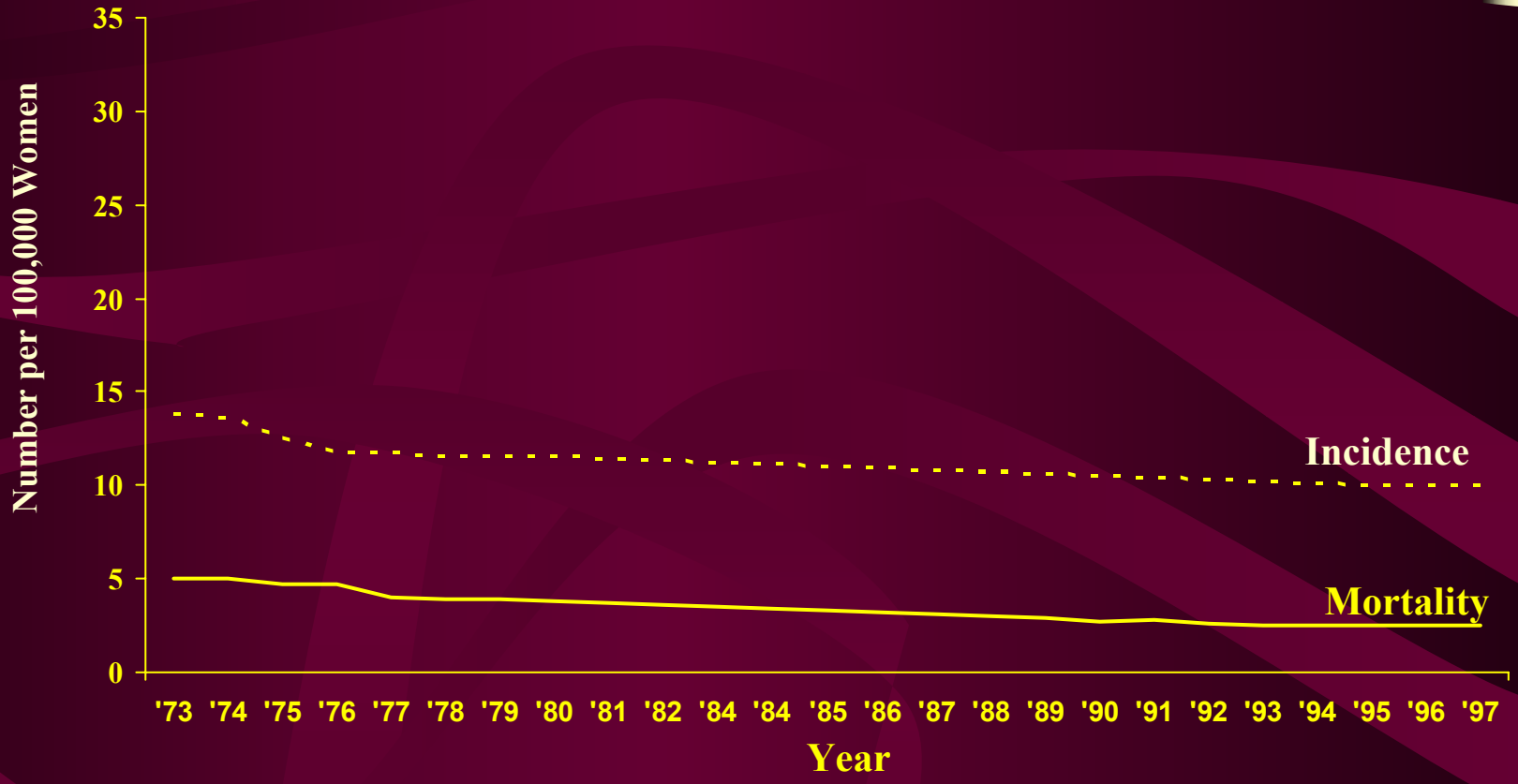



Obscuring Blood

Neoplasia

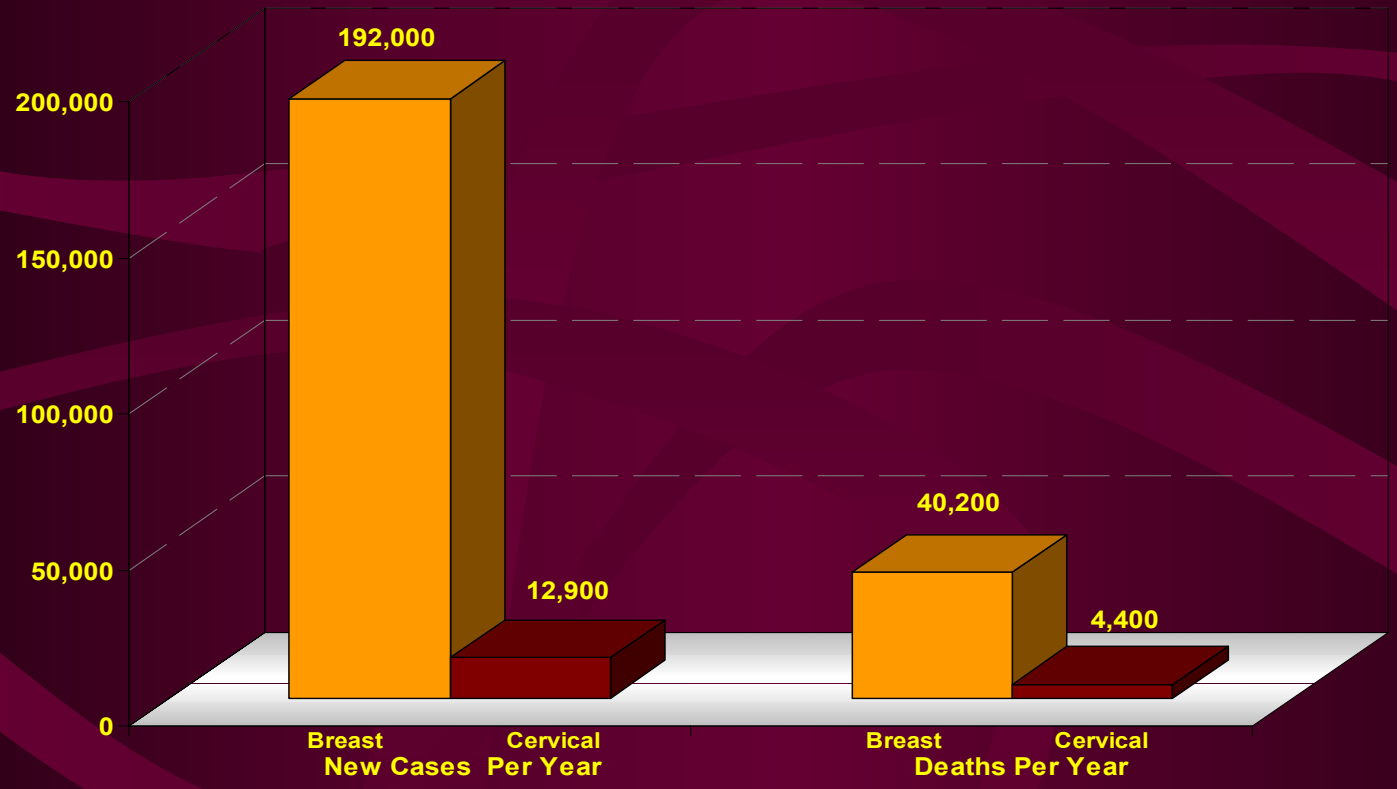
- 1940 Cervical Cancer was the Leading cause of death from neoplasia in Women
- Risk Factors
- Modern Theory for Cervical Cancer

Incidence and mortality for cervical cancer, United States, 1973–1997



Rate is age-adjusted to 1970 U.S. population
Source: Cancer Statistics Review, 1973–1997

Incidence and mortality for cervical cancer, United States, 2000



Source: American Cancer Society, 2000

Healthy People 2010

- Objective 3.4: reduce the death rate from cancer of the uterine cervix
  - Baseline: 3.0 deaths per 100,000 females in 1998
  - Target: 2.0 deaths per 100,000 females in 2010

Source: U.S. Department of Health and Human Services, 2000.

Cervical Cancer Policy

- Increase screening of never and rarely screened women
- Decrease overscreening of women
- Provide appropriate follow up for abnormal Pap test results

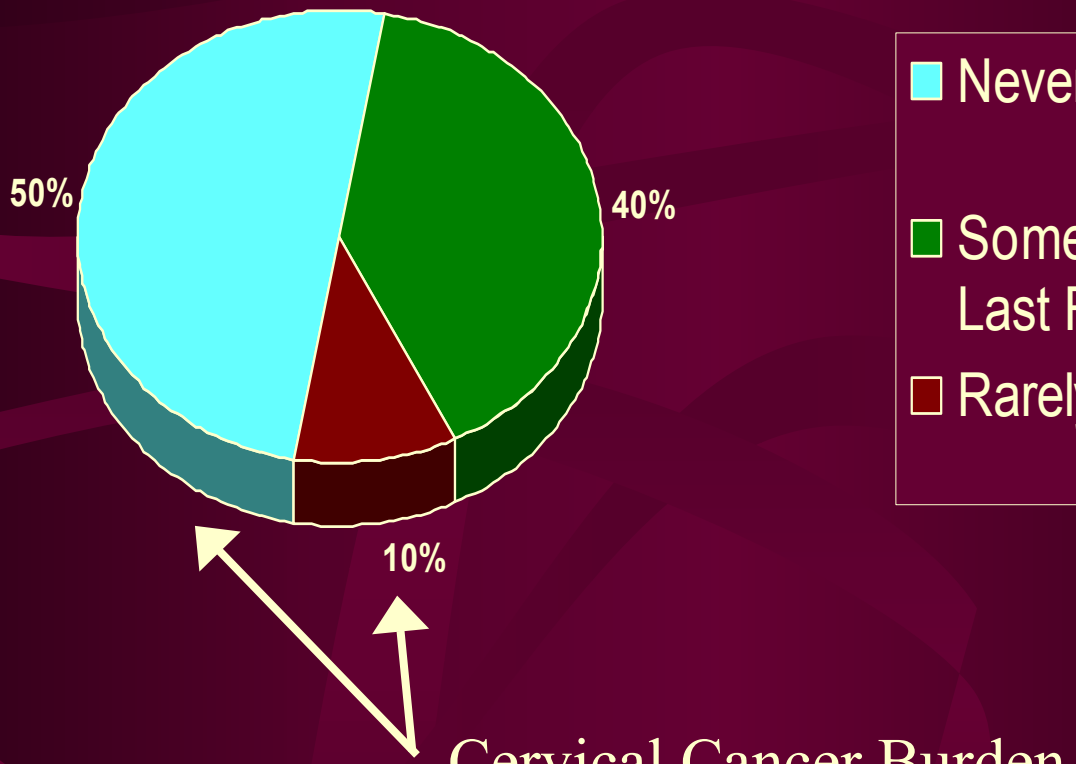
Cervical Cancer Policy: Other Issues

- Reducing Pap tests after hysterectomy
- Using new technologies
  - Liquid-based Pap tests
  - HPV testing

Policy Focus

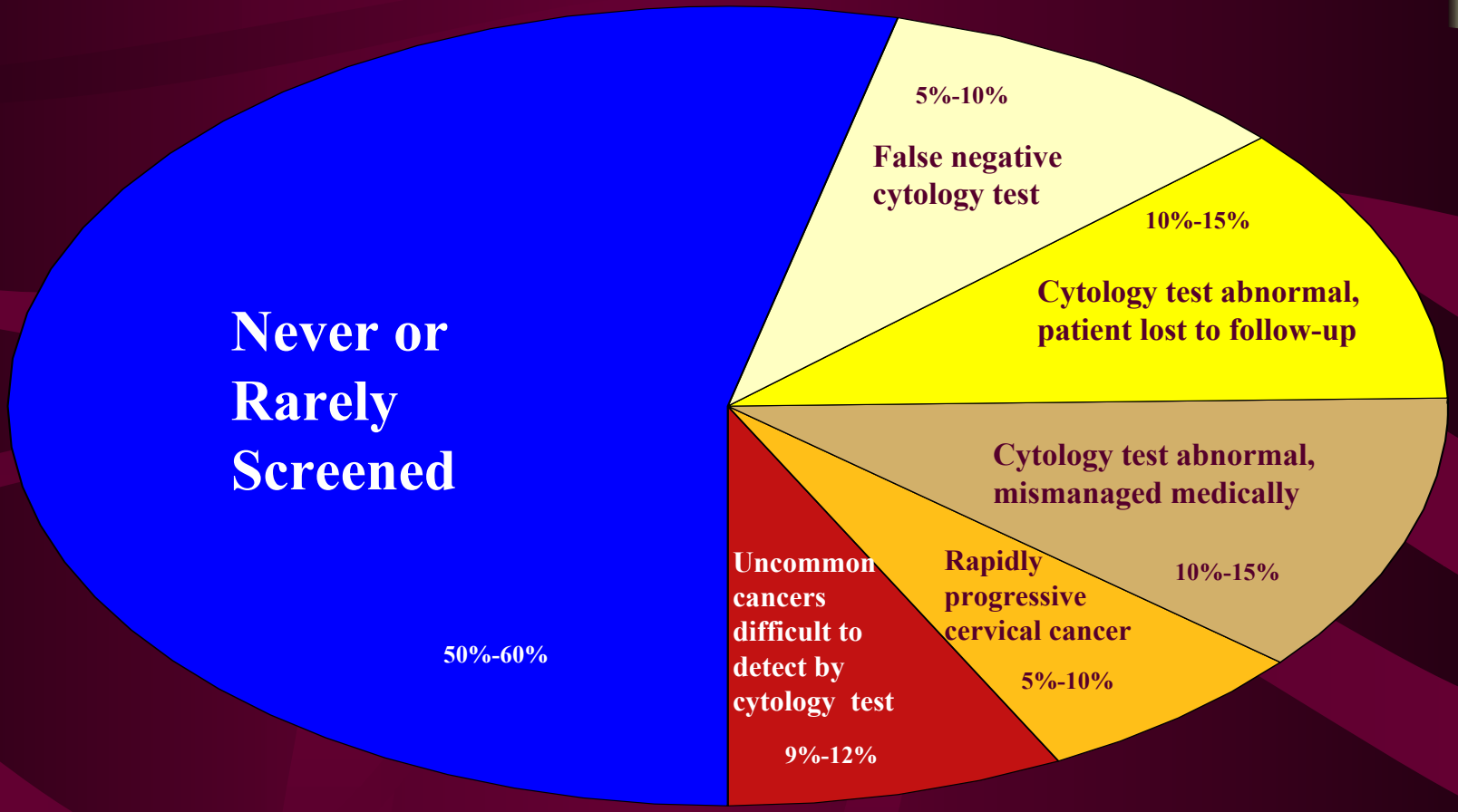
- Reaching never- and rarely-screened women.

Unequal Burden of Disease



Source: Shingleton et al., 1995

Unequal Burden of Disease



Sources:
NIH Consensus Conference
Janerich, Connecticut
Sung, California

Rarely Screened

- Of the 13,000 women who develop cervical cancer each year:
  - 50% never had a pap smear or more than 15 years
  - 10% haven't had a pap smear in 5 years
  - 10% had inappropriate triage
  - Remaining 30% are from errors in sampling and interpretation

Characteristics of women never or rarely screened for cervical cancer

- Older
- Low SES and/or lack of insurance or ability to pay for screening
- Less educated
- Racial or ethnic minority or new immigrant
- No regular health care provider
- Live in culturally-isolated urban neighborhoods or hard-to-reach rural areas

Reasons Women Aren't Screened

- Access
- Provider knowledge/behavior
- Patient knowledge/behavior

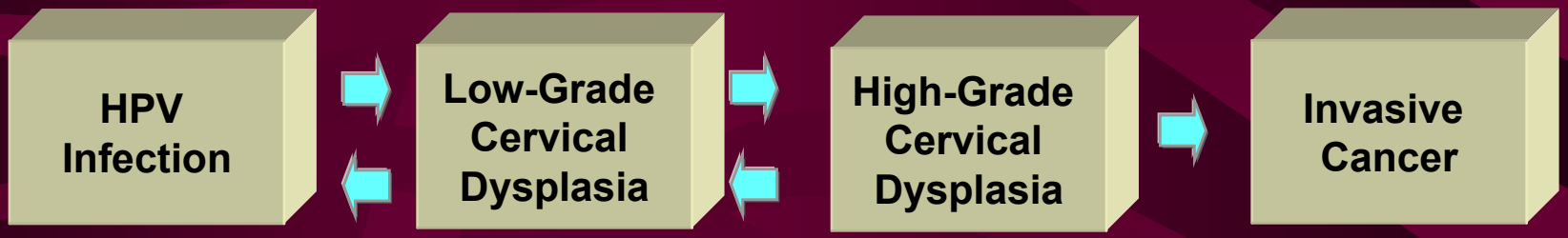
CDC Policy: Reducing over screening

- After a woman has had three, consecutive, normal Pap tests within a 5-year (60-month) period documented, the Pap test shall be performed every 3 years.

Evidence for need to reduce over-screening

- Natural history of cervical cancer
- The effectiveness of the Pap test as a screening tool
- Data analysis
- Policies/guidelines from other professional organizations

Natural history of cervical cancer



Source: PATH, 2001

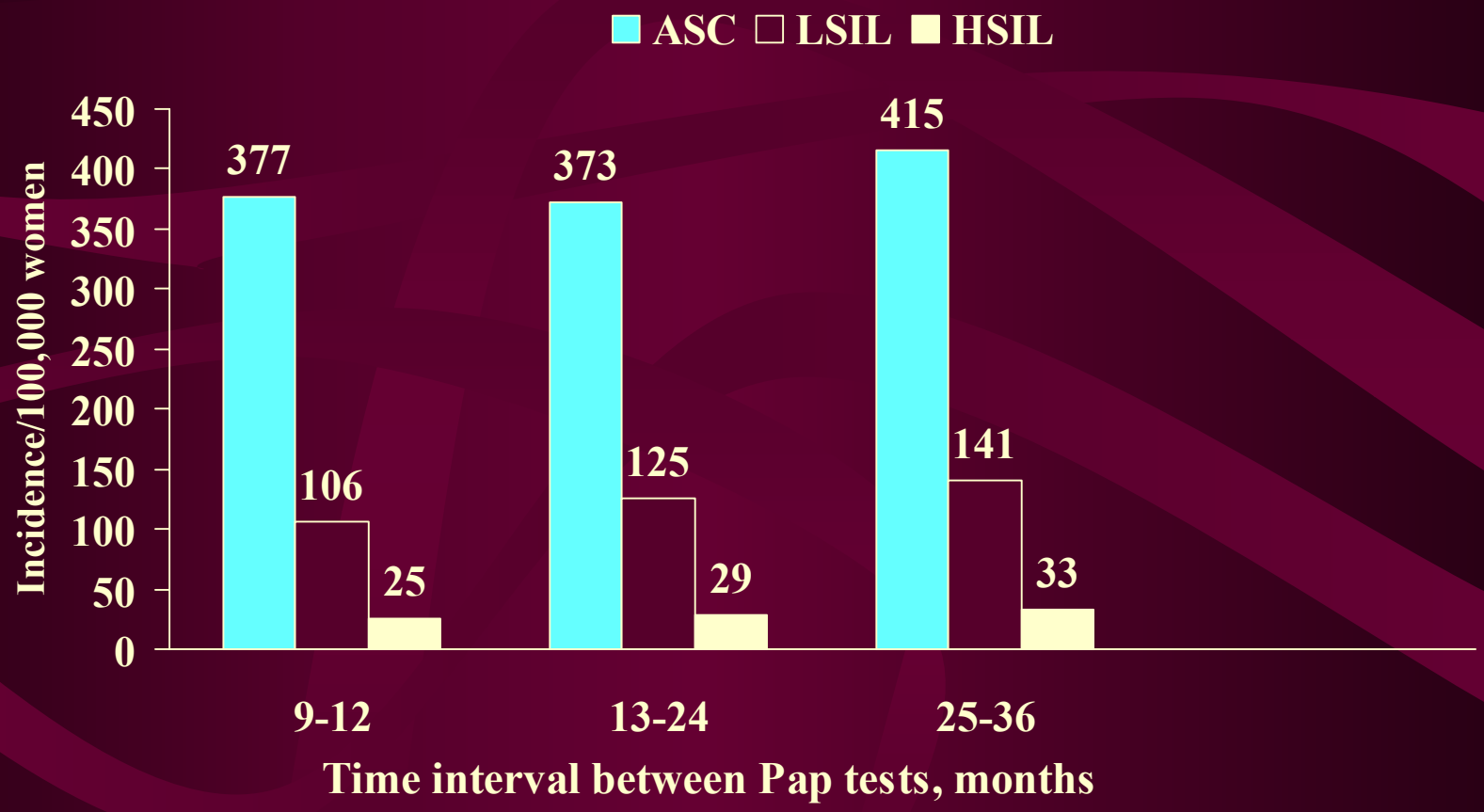
Overall Rescreening Results

- Results of a 2nd Pap test following a normal Pap test—
  - Benign — 121,576 (94.4)
  - Abnormal — 5,856 (4.6)
    - ASC — 4,432 (3.4)
    - LSIL — 1,140 (0.9)
    - HSIL — 271 (0.2)
    - Suggestive of squamous cell cancer — 13 (0.0)

Source: Sawaya et al., 2000

Rescreening Results by Time Interval

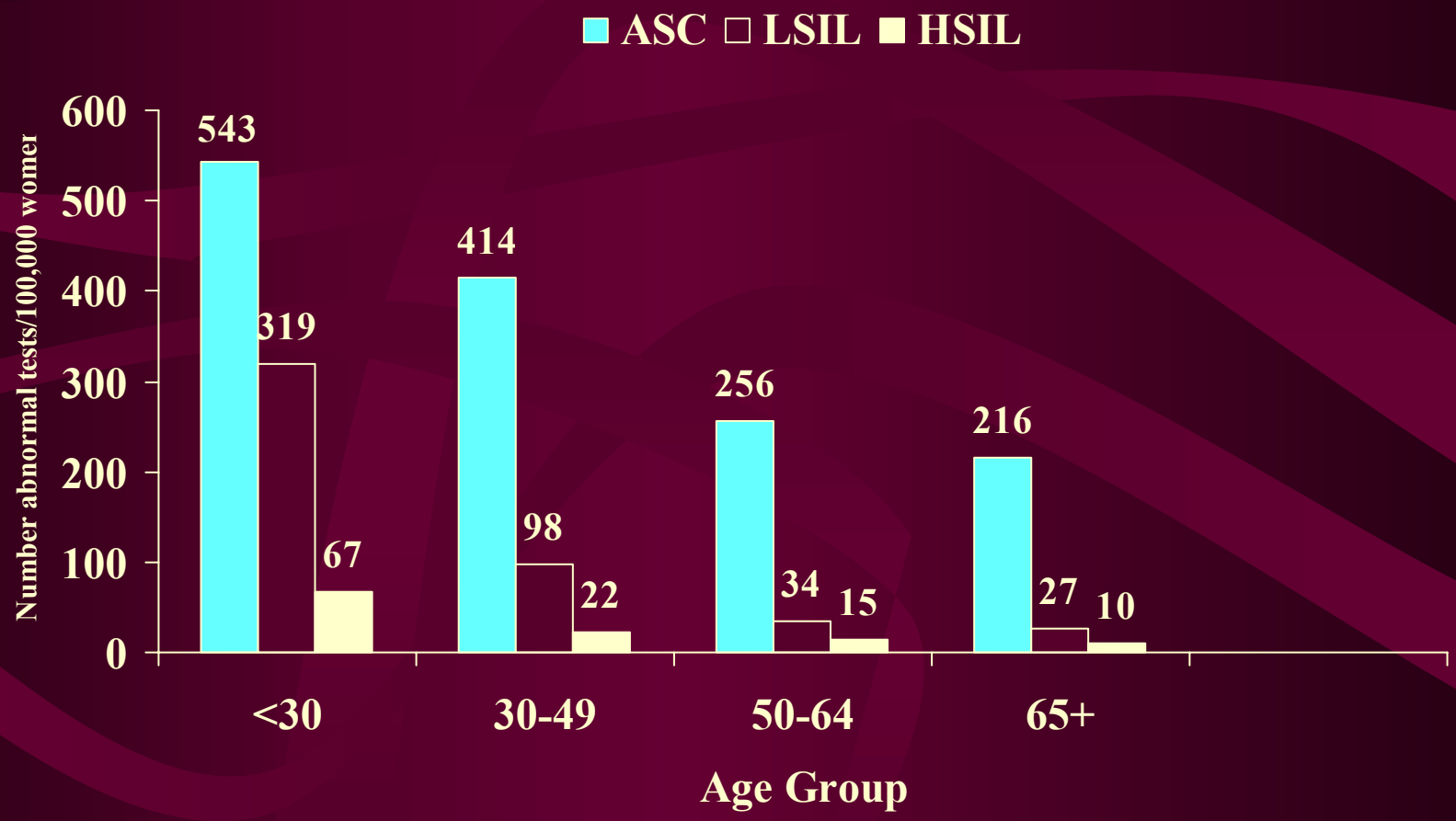
Age-adjusted incidence rates of cytological abnormalities for various screening intervals;128,805 women screened through the NBCCEDP, 1991–1998.



Source: Sawaya et al., 2000

Rescreening Results by Age

Cytological abnormalities within three years of a normal Pap test, per 100,000 women, by age; 128,805 women screened through NBCCEDP, 1991–1998.



Source: Sawaya et al., 2000

NBCCEDP Study Conclusions

- Pap test abnormalities are uncommon
- False positive testing may increase morbidity from unnecessary diagnostic evaluations without decreasing mortality.

Source: Sawaya et al., 2000

Existing Screening Guidelines

- WHO (1992): Annual Pap tests are often unnecessary—"it is clear that it is more cost-effective to recruit a high proportion of the population and screen them infrequently, than to recruit a low proportion and screen them often."

Existing Screening Guidelines (continued)

- USPSTF (1996): “There is little evidence that women who receive annual screening are at significantly lower risk for invasive cervical cancer than are women who are tested every 3–5 years.”

Existing Screening Guidelines (continued)

- ACPM (1996): “Estimates from mathematical models indicate that regular triennial screening would achieve 91-96% of the benefit of annual screening, while greatly reducing the cost, potential harms, and inconvenience.”

Existing Screening Guidelines (continued)

- ACOG (2000): “After a woman has had three or more consecutive, satisfactory, annual cytological examinations with normal findings, the Pap test may be performed less frequently on a low-risk woman at the discretion of her physician.”
- ACS (2001): “After three or more consecutive annual exams with normal findings, the Pap test may be performed less frequently at the discretion of the physician.”

CDC Policy: Pap Tests After Hysterectomy

- Cervical cancer screening in women after a hysterectomy is not necessary unless the hysterectomy was done for cervical neoplasia.

Pap Tests After Hysterectomy (continued)

- USPSTF (1996): "Women who have undergone hysterectomy in which the cervix was removed do not require Pap testing, unless it was performed because of cervical cancer or its precursors."

CDC Policy: New Pap Testing Technologies

- NBCCEDP funds may not be used to reimburse for liquid-based technologies approved by FDA for primary screening unless the reimbursement rate for the new technology does not exceed the current reimbursement rate for a conventional Pap test.
- Use of new technologies to be re-evaluated when new data are available.

What We Know About Liquid-based Testing Technologies

- More sensitive, but not more specific, than conventional Pap tests (Austin, 1998)
- ACOG did not recommend routine use in 1998:
  - Cost too high
  - Insufficient data demonstrating reduction of disease incidence or cancer survival
  - Currently silent on the issue

CDC Policy: HPV/DNA Testing

- Until further evidence is available, NBCCEDP funds may not be used to reimburse for HPV/DNA tests.
- Policy is being re-examined as new firm evidence becomes available.

HPV/DNA Testing

- ALTS Trials
  - No benefit for women with LSIL results
  - Probable benefit for women with ASC results

Review: Major Policy Emphasis

- Increase screening of never- and rarely-screened women
- Decrease unnecessary over-screening of women

Policy Implementation Challenges

- Reaching never- and rarely-screened women
- Encouraging providers to reduce overscreening

Challenge: Encouraging changes in provider practice to reduce over-screening

- Concerns
  - Potential for a two-tiered program
    - Low SES is correlated with not being screened for cervical cancer.
    - NBCCEDP has the opportunity to reduce the disparity between low and high SES.
  - Providers will lose women if they do not come in for their yearly Pap test
    - Eligible women can return annually for a CBE and mammogram (if age-appropriate).

Challenge: Encouraging changes in provider practice to reduce over screening (continued)

- Concerns (continued)
  - Clinicians disagree about screening intervals
    - Disagreement among clinicians about screening intervals is common.
    - Programs can consult with Medical Advisory Committees to determine the screening frequency parameters.
    - Screening interval for other preventable cancers not the same as for breast and cervical cancer

Next Steps

- Continued CDC support as programs implement the policy
  - Provide technical assistance
  - Help programs develop tools to communicate with providers and patients
  - Identify effective patient recruitment strategies
- Explore and evaluate impact of policy implementation
- Continue a national dialogue with guideline and policy developers

Key Messages

- Incidence and mortality rates for cervical cancer have leveled off.
- A decrease in cervical cancer incidence can be achieved by identifying and screening women never- or rarely-screened.
- The greatest risk for developing cervical cancer is not being screened.

What Can You Do?

- Educate your colleagues
- Talk to other programs
- Promote a simple message regarding overscreening

2001 Bethesda System, simplified

- Specimen Adequacy
- General Categorization (optional)
- Interpretation/result
- Other Malignant Neoplasms (as appropriate)
- Automated review and Ancillary Testing (as appropriate)
- Educational Notes and Suggestions (optional)

2001 Bethesda System, simplified

- Specimen Adequacy
  - Satisfactory for evaluation
  - Unsatisfactory for evaluation

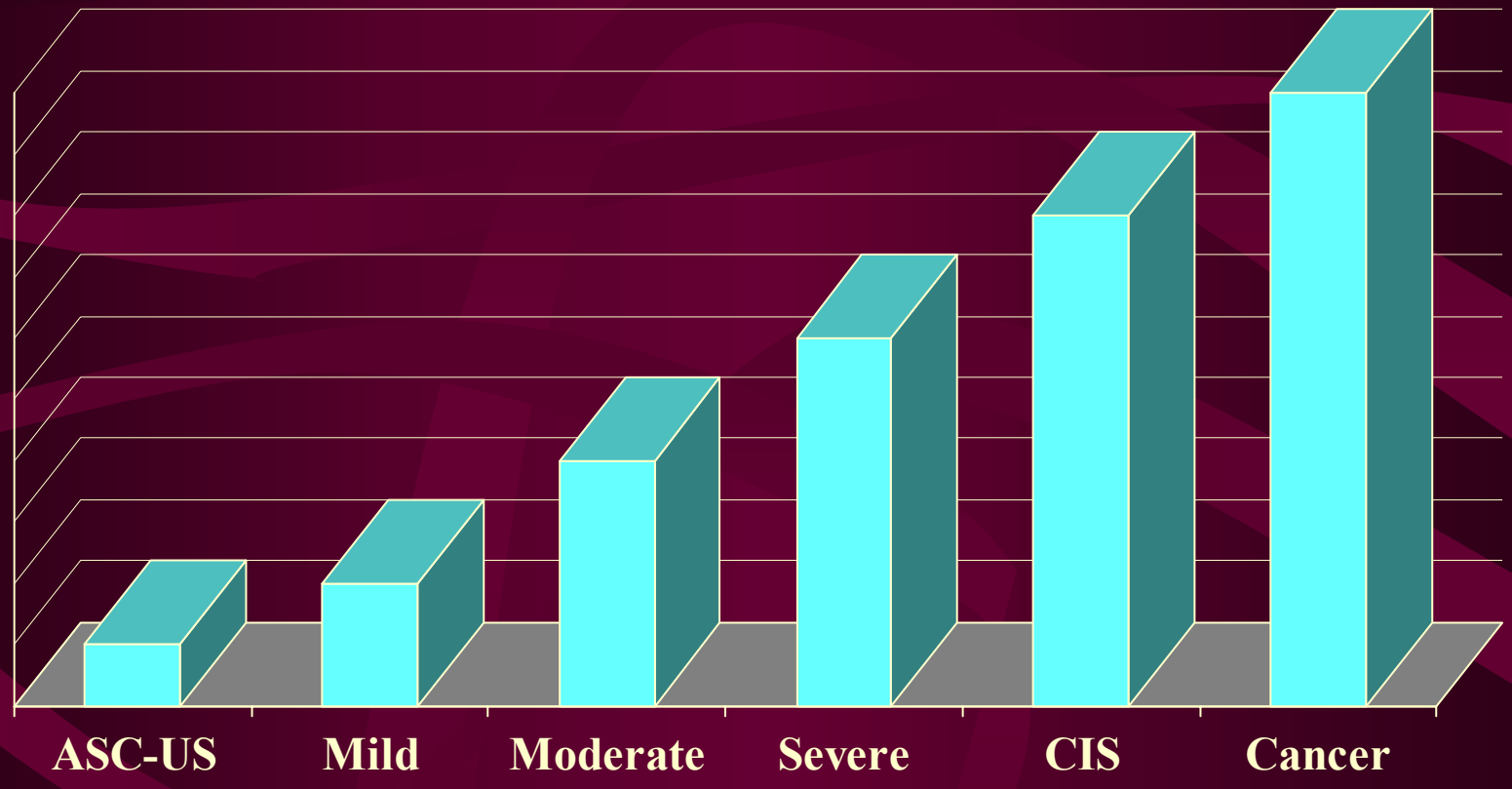
2001 Bethesda System, simplified

- General Categorization (optional)
  - Comments for overall evaluation
    - "within normal limits" replaced by "negative for intraepithelial lesion or malignancy
  - Most common is "presence of endometrial Cells"

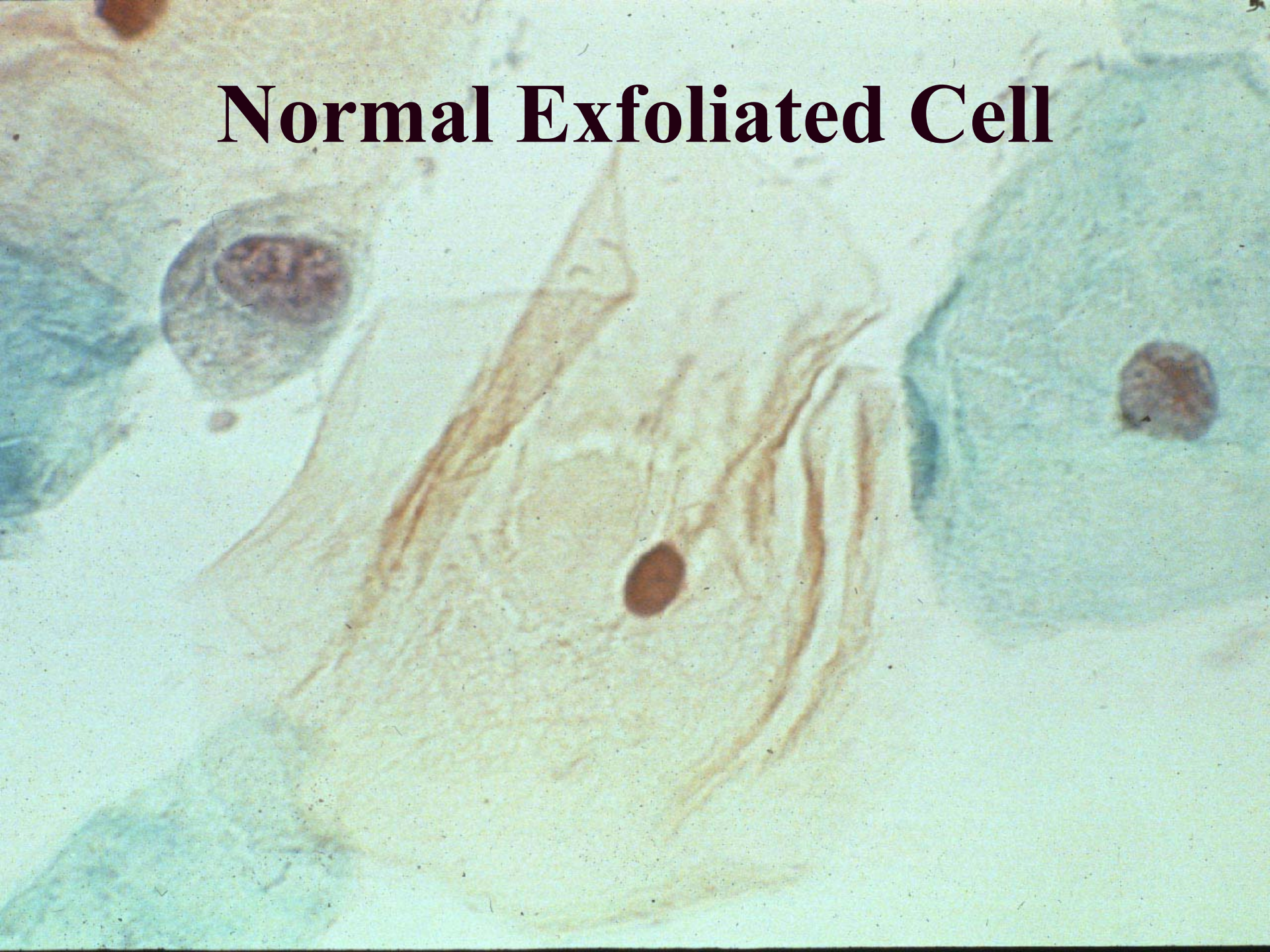
Bethesda System

- Squamous Cell
  - Atypical Squamous Cells
    - Undetermined Significance (ASC-US) (2002 Change)
    - Cannot Exclude High Grade (ASC-H) (2002 Change)
    - HPV-LGSIL
    - LGSIL(CIN I, Mild Dysplasia)
    - HGSIL(CIN 2 (Moderate Dysplasia) and CIN 3 (Severe Dysplasia))
    - CIS
    - Squamous Cell Carcinoma
- Atypical Glandular Cells (AGC) (2002 Change)
  - Adenocarcinoma

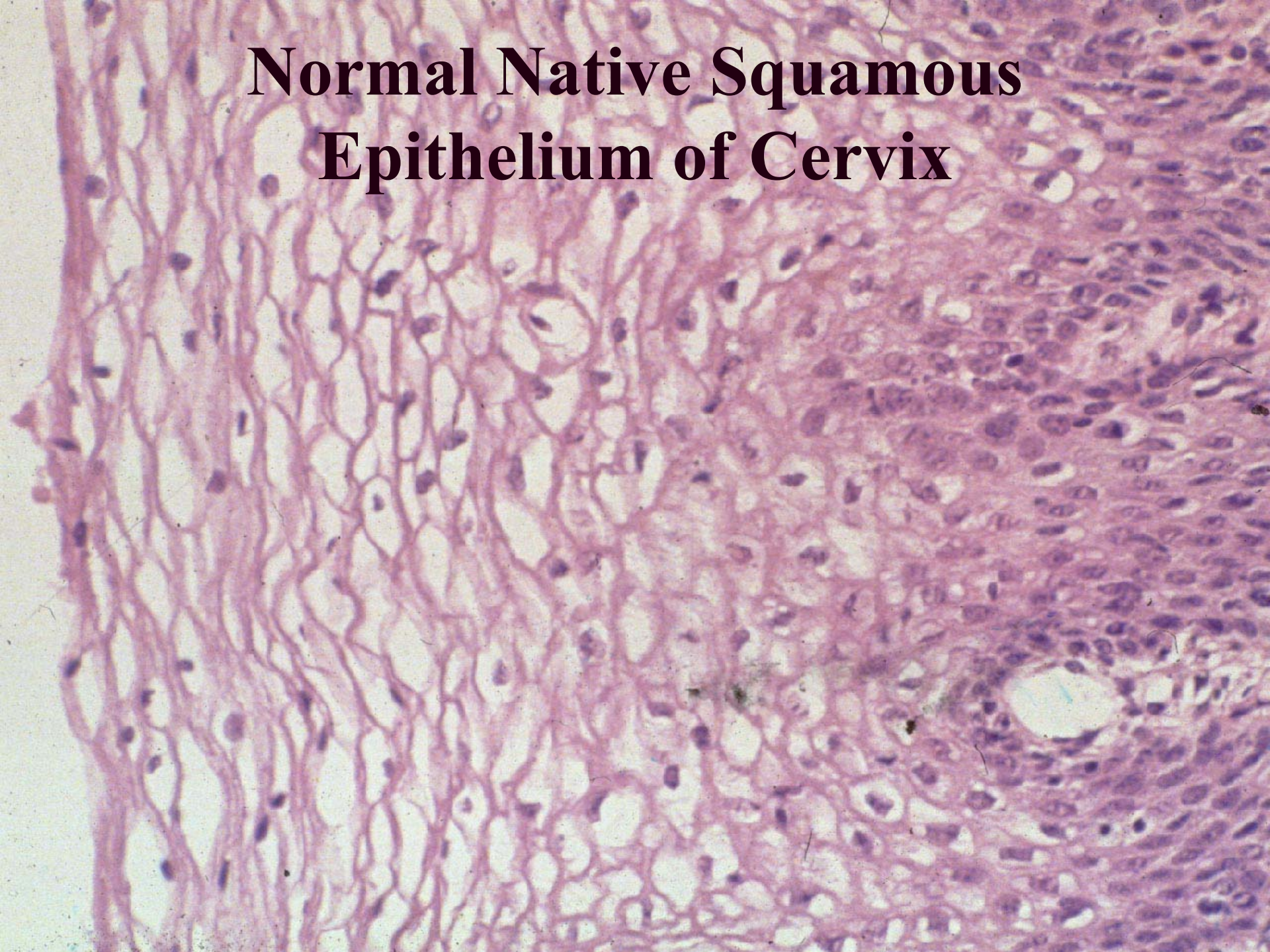
Bethesda System



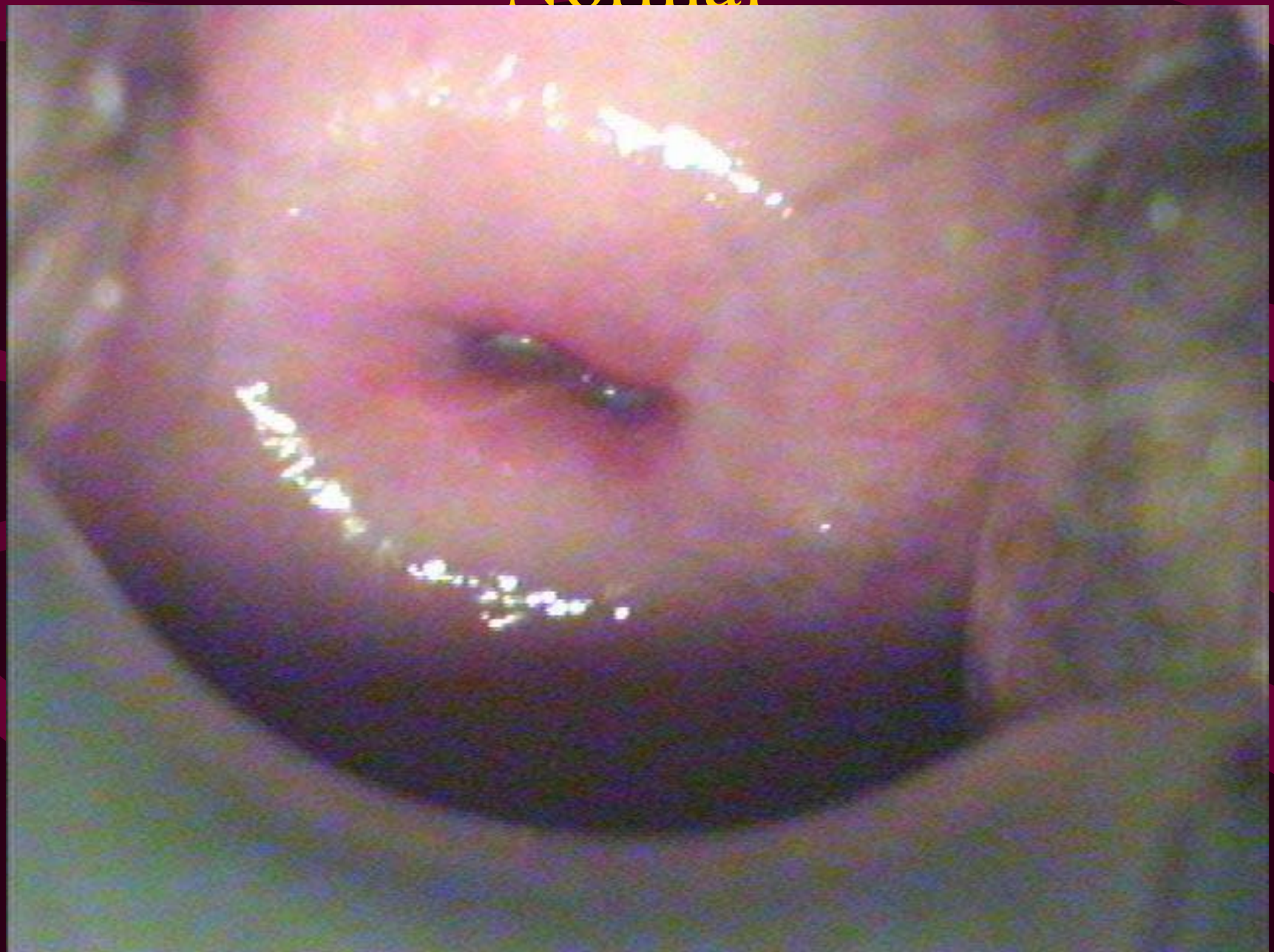
Normal Exfoliated Cell



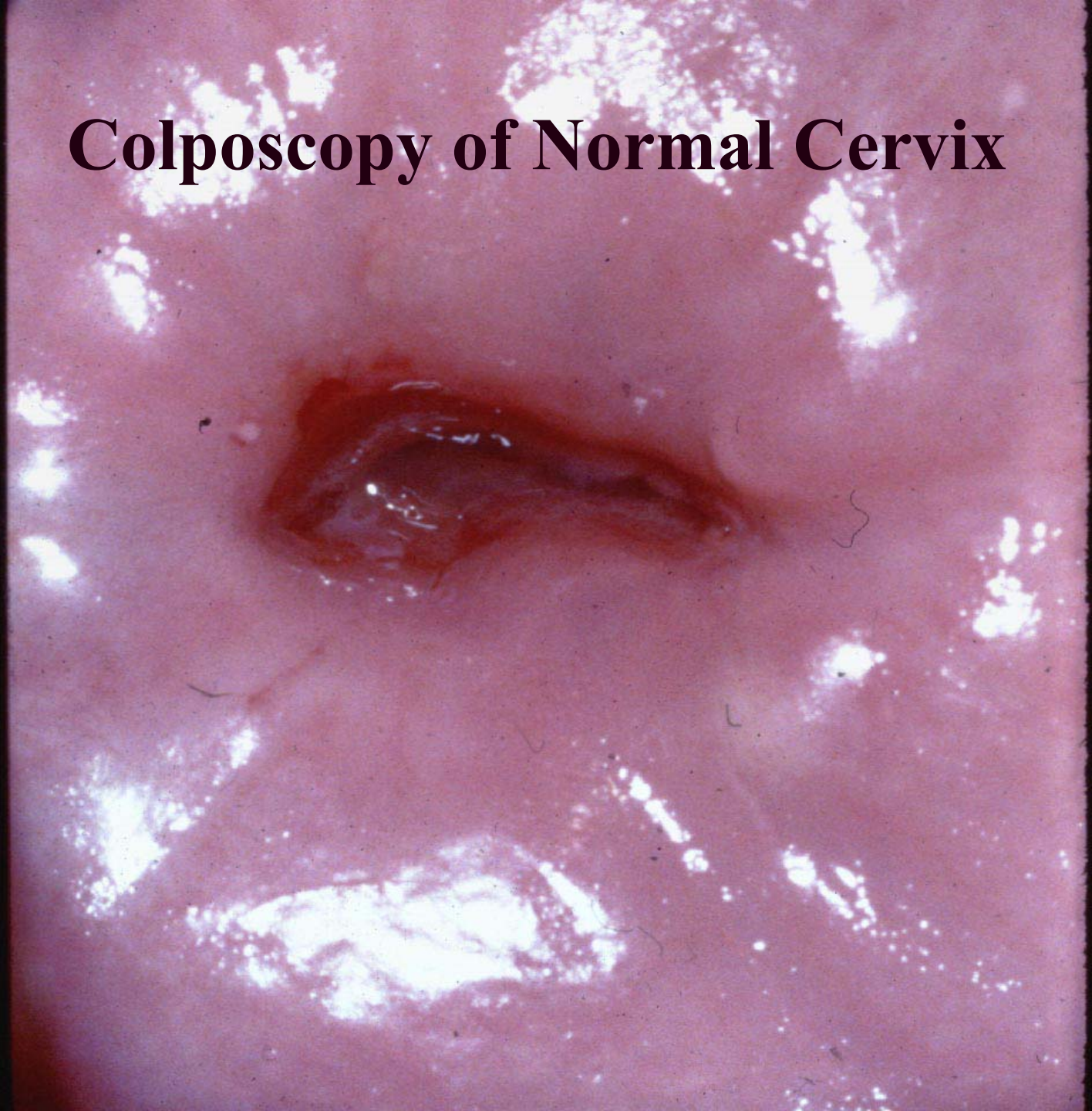
Normal Native Squamous Epithelium of Cervix



Normal



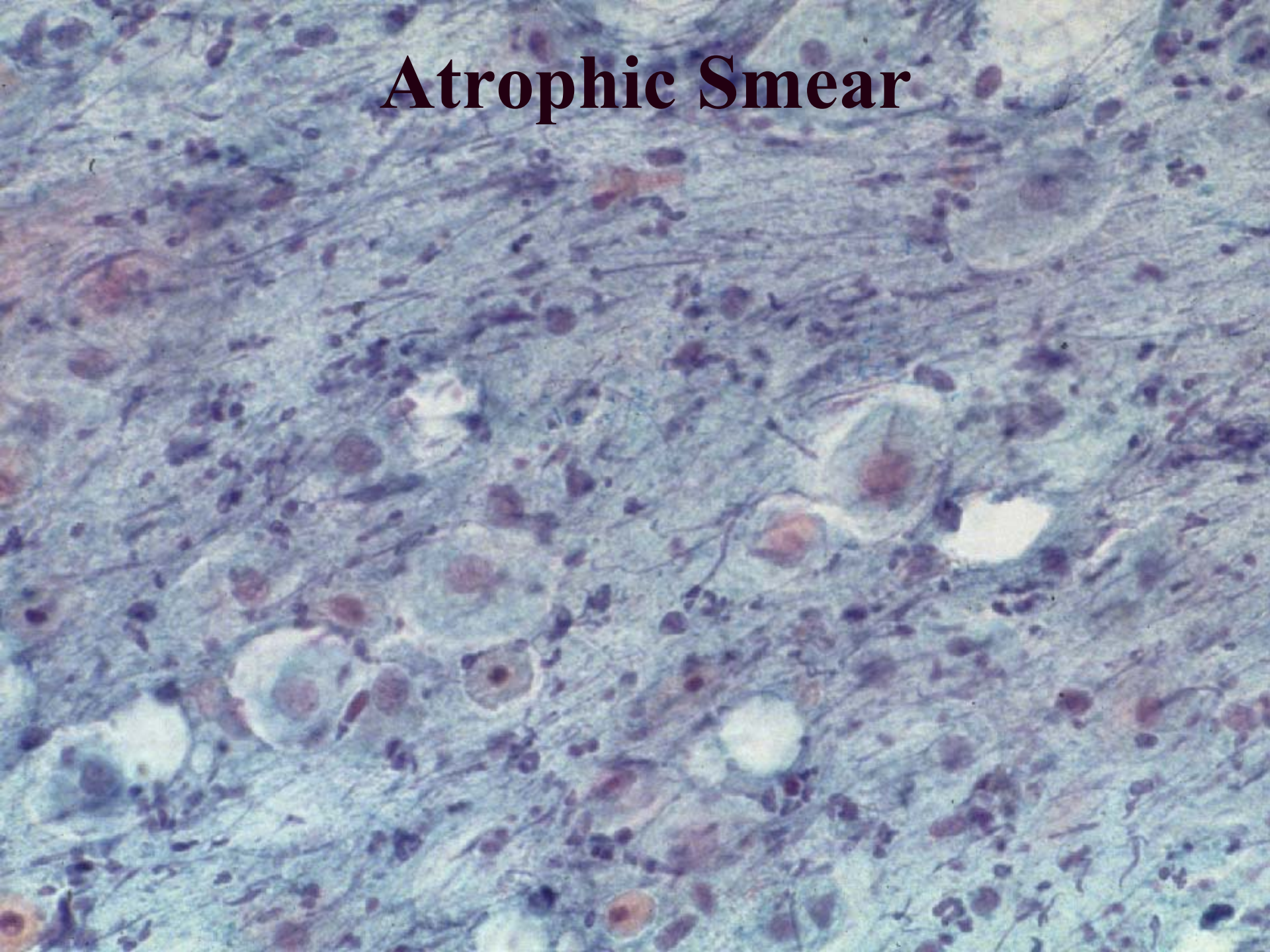
Colposcopy of Normal Cervix



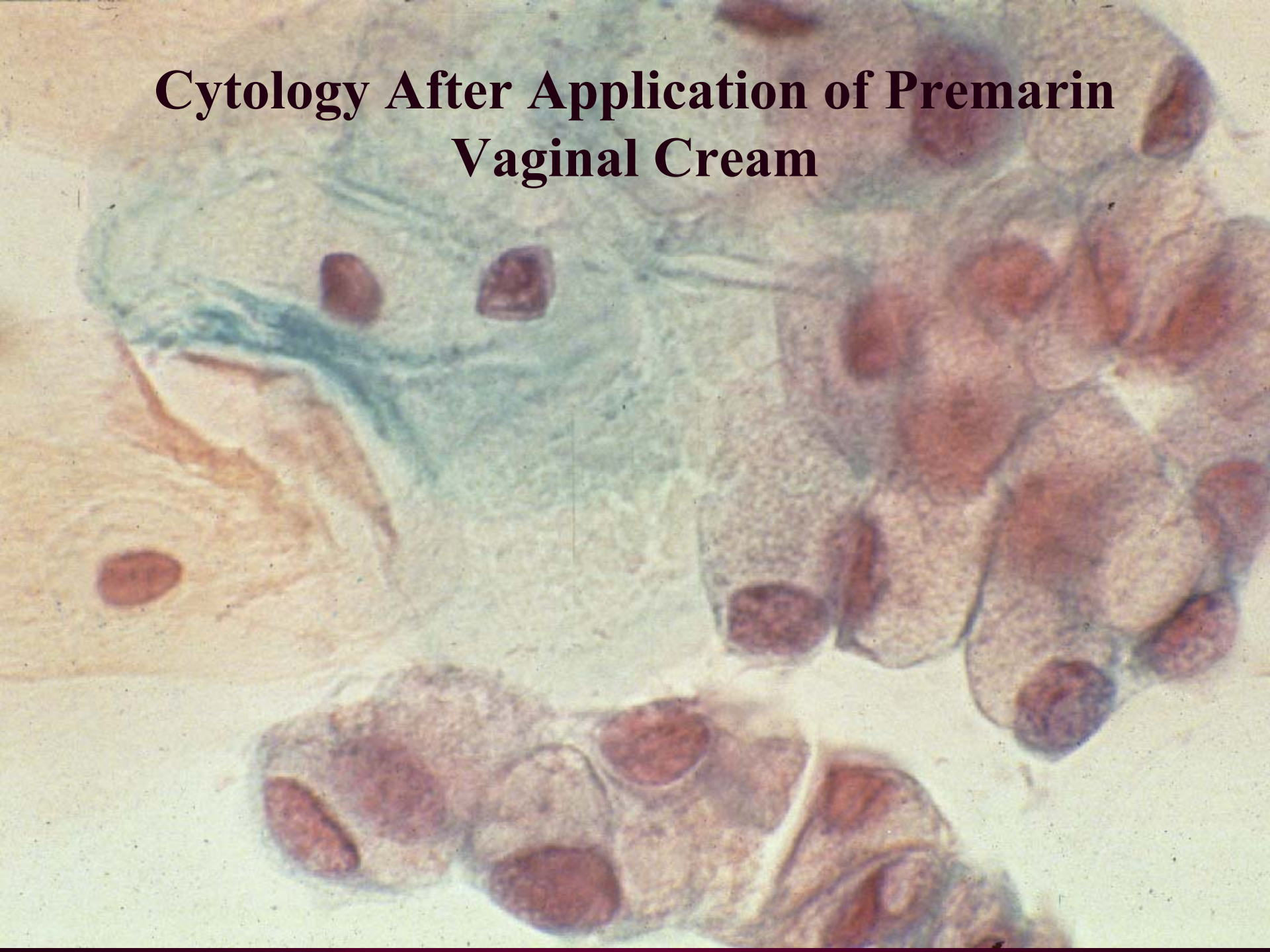
Cytology of Normal Endocervical Cells

Cytology of Menstrual Smear

Atrophic Smear



Cytology After Application of Premarin Vaginal Cream



Conclusions on Pap Smears

- Correct collection technique
- Know your Pathologist
- Follow up procedures

Break